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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

MAY 19 2004

PCT

To:
PAUL K. LEGAARD
WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE-46TH FLOOR
PHILADELPHIA, PA 19103

DUE DATE
MAX DATE
DOCKETED BY

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

RECEIVED MAY 2004

MAY 17 2004 (PCT Rule 71.1)

DOCKET DEPT. WWKMAN

Date of Mailing (day/month/year) 12 MAY 2004

Applicant's or agent's file reference		IMPORTANT NOTIFICATION
IBIS-0420 DIBIS-0003WO		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US02/20336	26 June 2002 (26.06.2002)	26 June 2001 (26.06.2001)

Applicant

ISIS PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Ardin Marschel Janice Ford for Telephone No. 703-308-0196

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IBIS-0420	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/20336	International filing date *(day/month/year)* 26 June 2002 (26.06.2002)	Priority date *(day/month/year)* 26 June 2001 (26.06.2001)
International Patent Classification (IPC) or national classification and IPC IPC(7): G01N 33/48 and US Cl.: 702/19		
Applicant ISIS PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24 January 2003 (24.01.2003)	26 April 2004 (26.04.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Ardin Marschel Telephone No. 703-308-0196

Janice Ford for

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/20336

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-36 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 37-41, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-29, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-2, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/20336

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is
   - ☐ complied with.
   - ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must normally be paid, however, no invitation to pay has been set forth at this time.

Group I, claim(s) 1-10, drawn to methods of identifying an unknown bioagent using a database, product amplification, molecular mass determination, nad comparison to known bioagents.

Group II, claim(s) 11-15, drawn to databases having cell-data positional significance for the alignment and non-alignment of data-containing cells for designating a structural feature of a polymer.

Group III, claim(s) 16, drawn to methods of reconciling first and second files involving cell-data records, a backup file, a reconcile file, and copying various files.

Group IV, claim(s) 17-25, drawn to a service for providing information related to a bioagent utilizing a database of masses and delivering a response to a requester from a master file.

Group V, claim(s) 26-35, drawn to methods of determining a geographical origin of a selected bioagent using a database of molecular masses.

The inventions listed as Groups I - V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The Special Technical Features of each of the Groups I - V are distinct as summarized in the above descriptions for each Group. It is noted that each Group is directed to a different and distinct Special Technical Feature.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
   - ☒ all parts.
   - ☐ the parts relating to claims Nos. ____

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/20336

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-10 and 17-35	YES
	Claims 11-16	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-35	NO
Industrial Applicability (IA)	Claims 1-35	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 7 and 32 are objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: The word "electorospray" is misspelled in claims 7 and 32.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1-10 and 17-35 lack an inventive step under PCT Article 33(3) as being obvious over either of MARGERY et al. (U.S. Patent Number 6,055,487) or COLI et al. (U.S. Patent Number 6,018,713) in view of either of MUDDIMAN et al. (1997) or MUDDIMAN et al. (1996). Both of the descriptions of MARGERY et al. and COLI et al. are directed to the interactive ordering of testing at a central laboratory with computer network return of the test results as summarized in their respective abstracts and titles. COLI et al. in column 3, lines 1-5, lists tests available including microbiology. In lines 6-10 of column 3, of COLI et al. a user may retrieve the test information. The Internet and other networks are summarized in COLI et al. in column 9, lines 62-67, for use in communicating test results. LAN, WAN, and Internet communication of test data is also described in MARGERY et al. in column 6, lines 44-59. Various medical testing types are summarized as being useful regarding laboratory testing in the invention of MARGERY et al. in column 2, lines 59-63, directed to microbiology testing. In summary, both MARGERY et al. and COLI et al. describe central laboratory testing inclusive of microbiology testing which is a medical context motivates and suggests microbiology testing for microorganisms in medical samples. Both also describe the communication of test results over networks such as the Internet etc. Specific testing procedures, however, for microorganisms has not been set forth in these references and thus are motivated and suggested as being found elsewhere such as in the prior art.

The two MUDDIMAN et al. references both describe the usage of PCR with mass spectrometry for microorganism detection and identification in samples. Both references utilize recommended PCR primer sets for hybridizing to flanking conserved sequences to a targeted region of the nucleic acid to be detected as summarized in the respective abstracts. Figures 2 and 3 on page 3709 of MUDDIMAN et al. (1996) shows the characteristics of mass fregment spectra for at least two microorganisms which is at least a minimal dimensional master database for such masses for identification purposes thus providing a reasonable expectation of success for such identification generically. Table 1 on pages 3710 shows distinctive mass database values for 4 different microorganisms. A specific statement of taxonomic differentiation and thus identification is set forth in MUDDIMAN et al. (1996) on pages 3708, first column, last sentence of the second full paragraph, which clearly sets forth the recognition of such differentiation practice for identification of one microorganism from another. The two MUDDIMAN et al. references both also suggest and motivate the identification of geographical monitoring of microrganisms (as in instant claims 26-35) via discussion, for example, in MUDDIMAN et al. (1997) pages 1543-1544, bridging sentence, directed to monitoring of communities of soil and other environments.

Thus, it would have been obvious to the practitioner in the art at the time of the instant invention to be motivated to perform central laboratory testing for various medical issues including microbiology testing as set forth in MARGERY et al. or COLI et al. where the testing procedure usable in such a laboratory microorganism testing methodology is described in the prior art of either of MUDDIMAN et al. (1996) or MUDDIMAN et al. (1997) including a reasonable expectation of success for identifying microorganisms and their geographic origins thereby therefore resulting in the practice of the instant invention. Claims 1-35 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made and used in industry because they are directed to microbiology testing which is useful in medical practice as well as database and file management invention which is useful in computer processing.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Claims 11-13 lack novelty under PCT Article 33(2) as being anticipated by MUDDIMAN et al. (1997). MUDDIMAN et al. describes nucleic acid base compositions in Table 1 on page 1547 wherein aligned base compositions such as A, G, etc. are set forth in columns as well as non-aligned base compositions wherein differing numbers of bases such as A, G, etc. are set forth via the subscripting in the base compositions column. These aligned and non-aligned bases describe structural features of a polymer as well as many polymers in a region of sequence which is conserved via the priming utilized in PCR reaction in order to define the regions being analyzed via mass. See the abstract on page 1543 which summarizes the primer usage in PCR by which to define targeted regions via conserved linear segments which share homology to the primers as required in instant claim 12. Inter-species alignments as in claim 13 are shown in the Table via species analyzed therein such as B. thuringiensis vs. B. subtilis.

Claims 11-15 lack novelty under PCT Article 33(2) as being anticipated by ECKER et al. (U.S. Patent Number 6,221,587). ECKER et al. describes the identification of molecular interaction sites, especially in RNA, in the abstract. Figures 7 and 8 show tables for alignments of RNA structures as well as non-alignments via differing symbols therein. These alignments show conserved regions therein as described in column 2, lines 47-58, and column 12, lines 27-38, in vertical columns as in said Table as also required in the instant claims. Structural regions of secondary structure are aligned and analyzed as described in column 14, liens 1-11, including the instant claim 15 bulge or loop features. These descriptions anticipate the above listed instant claims.

Claim 16 lacks novelty under PCT Article 33(2) as being anticipated by either of KUCALA (U.S. Patent Number 5,727,702) or KUCALA (U.S Patent Number 5,832,489). Figures 2 and 3 of both of the KUCALA Patents depict the formation of a backup file which is generated with the results of comparisons, which is reasonably interpreted as a reconcile file. These Figures also show the copying of data to old calendars as required in the last two lines of instant claim 16. This is described in more detail in columns 2-5 wherein a summary in column 4, lines 1-37, also describes the invention of instant claim 16.

---------- NEW CITATIONS ----------

US 5,727,202 A (KUCALA) 10 March 1998, see especially Figures 2 and 3.

US 5,832,489 A (KUCALA) 03 November 1998, see especially Figures 2 and 3.

US 6,221,587 B1 (ECKER et al.) 24 April 2001, see especially columns 2-14.

US 6,055,487 A (MARGERY et al.) 25 April 2000, see the entire document.

US 6,018,713 A (COLI et al.) 25 January 2000, see the entire document.

MUDDIMAN et al., Length and Base Composition of PCR-Amplified Nucleic Acids Using Mass Measurements from Electrospray Ionization Mass Spectrometry, Analytical Chemistry, Volume 69, pages 1543-1549, issued 1997, see entire document.

MUDDIMAN et al., Characterization of PCR Products from Bacilli Using Electrospray Ionization FTICR Mass Spectrometry, Analytical Chemistry, Volume 68, Number 1, issued 01 November 1996, pages 3705-3712, see entire document.